



Positive Quality Intervention: Obinutuzumab (Gazyva®) for Chronic Lymphocytic Leukemia and Follicular Lymphoma

Description: The purpose of this PQI is to provide an outline on obinutuzumab and to provide guidance on clinical considerations for its optimal medication management.

Background: Obinutuzumab is an intravenously administered monoclonal antibody targeted against CD-20. It is FDA approved for use in combination with chemotherapy and as monotherapy in chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). Infusion-related reactions are the most frequent and serious adverse effect, requiring premedication 30-60 minutes prior to administration along with rate titrations.¹

CLL: The CLL11 study compared chlorambucil monotherapy, obinutuzumab plus chlorambucil, and rituximab plus chlorambucil in previously untreated patients (median age 73) with CLL and no co-morbidities. At median follow up, progression-free survival (PFS) was statistically significantly higher in the obinutuzumab arm at 28.9 months compared to 15.7 months in the rituximab arm (p<0.0001). Overall survival and overall response rate were also reported to be statistically superior in the obinutuzumab arm (p-value not reported however), with similar rates of infusion reactions between both arms.² Based on the results of this study along with others, obinutuzumab earned a recommendation in the first-line setting for elderly patients with CLL by NCCN.³

FL: Similarly, the phase III GALLIUM study compared rituximab-based chemotherapy with obinutuzumab-based chemotherapy in newly diagnosed FL patients. At 3-year median follow up, the obinutuzumab arm demonstrated a slightly higher PFS of 80% compared to the rituximab arm with 73.3% PFS (p=0.001). The study showed that obinutuzumab was associated with a greater incidence of grade ≥ 3 infusion-related events (12.4% vs 6.7%; no p-value reported) and infections due to hematologic toxicities (20% vs 15.6%; no p-value reported).⁴ Based on these results, obinutuzumab in combination with chemotherapy is recommended in the first-line setting for FL by NCCN.⁵

PQI Process: Upon order of obinutuzumab and prior to first and second infusion:

- Confirm correct patient, indication, dosing, and frequency

	CLL ¹ (in combination with chlorambucil)*	FL ¹
Dosing	Cycle 1: (Load dose) D1 – 100 mg IV D2 - give remaining 900 mg IV D8 and D15 - 1,000 mg IV; 28 day cycle	Cycle 1: 1,000 mg IV on D1, D8, and D15; 28 day cycle
	Cycle 2-6: 1,000 mg IV on D1; 28 day cycle	Cycle 2-6 ^{**} : in combination with bendamustine 1,000 mg IV on D1; 28 day cycle
		Cycle 2-6/8 ^{***} : in combination with CHOP (6 cycles) or CVP (8 cycles) 1,000 mg IV on D1; 21 day cycle
		Maintenance monotherapy: 1,000mg IV on D1; 2 month cycle for up to 2 years (start 2 months after previous dose)

*Other off-label dosing/combinations exist including but not limited to: acalabrutinib, ibrutinib, venetoclax; note that cycle frequency may differ

** Relapsed FL or FL refractory to a rituximab-containing regimen, followed by obinutuzumab monotherapy

*** Indicated for previously untreated stage II bulky, stage III or IV follicular lymphoma (FL) followed by 2 additional obinutuzumab monotherapy cycles

- Ensure orders are placed for appropriate required premedications to prevent infusion reactions¹
 - **H₁-antagonist** (diphenhydramine 50 mg IV/PO) – administer at least 30 minutes prior¹
 - **Acetaminophen** 650-1000 mg PO – administer at least 30 minutes prior¹
 - **Corticosteroid** (dexamethasone 20 mg or methylprednisolone 80 mg IV) (hydrocortisone is not recommended as it has not been effective) – administer at least 60 minutes prior^{1,3,5}
 - Week 3: Provider may opt to omit premedications if no previous reactions¹
- Review vitals and laboratory values – at regular intervals with each dose and as clinically indicated^{1,3,5}
 - Monitor current CBC w/ diff, CMP

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- Electrolytes, phosphate, uric acid, LDH, renal function for tumor lysis syndrome (TLS)
- Screen for appropriate supportive therapies prior to first dose and ensure orders are placed^{3,5,6}
 - **Hepatitis B status:** review surface antigen/core antibody for prior infection/risk for reactivation
 - **TLS prophylaxis:** prophylactic hydration and antihyperuricemic (allopurinol) if high risk¹
 - **PJP pneumonia prophylaxis:** (sulfamethoxazole/trimethoprim)⁶
 - **Antiemesis:** at least one medication for breakthrough emesis⁷
- Address correct titration rate on orders based on dose number and infusion-related reactions:¹

	CLL ¹	FL ¹
Week 1	Day 1: 25 mg/hour over 4 hours. No titration. Day 2: If no infusion reactions with day 1: initiate rate at 50 mg/hour (25 mg/hour if infusion reaction occurred); may increase rate by 50 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour	Initiate at 50 mg/hour; may increase by 50 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour.
Week 2	If no infusion reactions, initiate at 100mg/hour (50 mg/hour if infusion reaction occurred); may increase rate by 100 mg/hour every 30minutes to a maximum rate of 400 mg/hour.	If no infusion reactions \geq grade 1 with dose 1: initiate rate at 100mg/hour; may increase rate by 100 mg/hour every 30 minutes as tolerated to a MAX rate of 400 mg/hour. Optional: If no grade 3 infusion reactions, may utilize a 90 minute infusion: 100 mg/hour for 30 minutes; then infuse at 900 mg/hour for 60 minutes with continued premeds.
Week 3 and beyond	Initiate at 100 mg/hour; may increase rate by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.	See week 2 titration rates.

- Vials come in 1000 mg/40 mL intravenous solution which must be stored at 2-8°C and protected from light *Note: preparation of medication varies depending on indication and dose number
 - 100 mg doses in 100 mL NS; use immediately
 - 900 mg dose in 250 mL NS; may store at 2-8°C for up to 24 hours
 - 1,000 mg dose in 250mL NS; may store at 2-8°C for up to 24 hours
 - Administer through a dedicated IV line (PVC or non-PVC administration set; do not mix with other medications; incompatible with dextrose or any diluents)¹
- Review concomitant treatment medications in regimen as necessary

Patient Centered Activities:

- Provide printed and verbal education with calendar of treatment schedule and follow-up appointments
 - Cover common short and long-term adverse reactions
 - Advise that medication may cause hepatitis B reactivation¹
- Ensure prophylactic prescriptions (TLS, antiemetic, antibacterial, antiviral, antifungal) are picked up
- Emphasize signs/symptoms of infusion-related reactions with where to go and whom to call
- Neutropenic precautions due to potential bone marrow suppression and/ or infections

References:

1. [Gazyva \(obinutuzumab\) \[prescribing information\]](#)
2. Goede, V., et al. (2014). Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *The New England journal of medicine*, 370(12), 1101–1110.
3. National Comprehensive Cancer Network. *Chronic lymphocytic leukemia/small lymphocytic lymphoma* [PDF]. NCCN.
4. Marcus, R., et al. (2017). Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *The New England journal of medicine*, 377(14), 1331–1344.
5. National Comprehensive Cancer Network. *B-Cell Lymphomas* [PDF]. NCCN.
6. National Comprehensive Cancer Network. *Prevention and Treatment of Cancer-Related Infections* [PDF]. NCCN.
7. National Comprehensive Cancer Network. *Antiemesis* [PDF]. NCCN.

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